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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,118	11/03/2005	Takashi Shinohara	239188	1727
23460 7590 06/10/2009 LEYDIG VOIT & MAYER, LTD TWO PRUDENTIAL PLAZA, SUITE 4900 180 NORTH STETSON AVENUE CHICAGO, IL 60601-6731				
EXAMINER				
TON, THAIAN N				
ART UNIT		PAPER NUMBER		
1632				
MAIL DATE		DELIVERY MODE		
06/10/2009		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/553,118

Applicant(s)

SHINOHARA ET AL.

Examiner

Thaia N. Ton

Art Unit

1632

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 March 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4 and 6-11 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4 and 6-11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/5508)
- Paper No(s)/Mail Date 3/5/09; 3/12/09
- 4) ☐ Interview Summary (PTO-413)
- Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Applicants' Amendment and Response, filed 3/5/09, has been entered. Claims 1 has been amended; claim 5 is cancelled; claims 1-4, 6-11 are under current examination.

The Shinohara Declaration has been considered.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-12) in the reply filed on 2/6/08 is acknowledged. The requirement is still deemed proper and is therefore made FINAL.

Claims 13-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/6/08.

Information Disclosure Statement

Applicants' IDS, filed 3/5/09 and 3/12/09, have been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 6-11 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of growing mammalian spermatogonial stem cells comprising growing mammalian spermatogonial stem cells for at least 3-4 weeks using a medium containing 1) GDNF or neurturin, 2) LIF, 3) EGF, 4) bFGF and 5) serum.

The specification does not reasonably provide enablement for using a medium containing only GDNF or neurturin and LIF absent any other growth factors or serum. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants' Arguments. Applicants argue that the relationship between GDNF family ligands and their receptors were clearly elucidated at the molecular level at the time the Application was filed, and that in particular, the cross talk of neurturin, artemin with the GDNF receptor and of GDNF with the neurturin and artemin receptors was well known in the art, and as such, one of ordinary skill in the art would recognize based on the teaching in the specification and what was known at the time of filing that the culturing medium for use in the inventive methods could include GDNF or equivalents thereto, such as neurturin and artemin. See p. 5 of the Response.

Response to Arguments. These arguments have been fully considered but are not fully persuasive. The Examiner notes that Example 3 of the specification provides enabling guidance for use of neurturin in place of GDNF in culturing spermatogonial stem cells. However, the scope of enablement includes the factors LIF, EGF, bFGF and serum in view of the working example, which shows that GS

cells were cultured in the same culture medium as Example 1 (see p. 43-44 of the specification). Additionally, the Examiner has considered Airaksinen *et al.*, however, it is noted that this article is primarily devoted to GFL signaling in neurons. Airaksinen states that GDNF was originally purified from rat glioma cell-line supernatants, and has other roles outside the nervous system, including a morphogen in kidney development and a regulator of differentiation in spermatogonia (see 1st paragraph). However, Airaksinen fails to provide a nexus between how GDNF's role in differentiation in spermatogonial is related to the roles of neurturin or artemin in spermatogonial differentiation. Thus, although neurturin, GDNF and artemin have been characterized with regard to their functions *in vivo*, this does not provide a nexus between this function and how it would function in culturing mammalian spermatogonial stem cells. That is, given that the Examiner has provided evidence to show that the culture conditions of spermatogonial stem cells has not been clearly elucidated in the art, particularly in view of the Creemers reference, which shows that utilizing some overlapping factors results in high percentages of cell death, and the specification, which teaches that there have been no successful attempts to grow SSCs *in vitro* to the extent that permits practical application, as well as the lack of guidance with regard to any other combination of factor(s) that would arrive at growing mammalian sperm stem cells, the enabled scope is determined to be with regard to neurturin or GDNF and additionally, LIF, EGF, bFGF and serum.

Applicants' Arguments. Applicants argue that the Shinohara Declaration shows that addition of growth factors, such as EGF and bFGF, is not necessary to achieve the growth of spermatogonial stem cells, and that the experiments that are set forth in the Declaration demonstrate that spermatogonial stem cells can grow in a medium containing GDNF and LIF without any other growth factors at a similar level to that achieved using a medium containing GDNF, LIF, EGF and bFGF. Applicants argue that at the time the Application was filed, it was well-known that

serum could be used for culturing various mammalian cells, and therefore it would be well-within the ability of the ordinarily skilled artisan

Response to Arguments. The Shinohara Declaration has been fully considered, but not fully persuasive. In particular, Example 1 of the Shinohara Declaration discusses culturing mouse spermatogonial stem cells under three conditions:

- 1) F/S medium containing EGF, bFGF, LIF and GDNF
- 2) F/S medium
- 3) F/S supplemented with GDNF and LIF

The Declaration teaches that after 5 days the cells were treated with trypsin and it was found that the cells can grow in a medium containing only GDNF and LIF. Although Example 1 of the specification does teach that the cells are capable of growing in a medium containing only GDNF and LIF, it is noted that the claims require that the cells can be cultured for 3 to 4 weeks, whereas the example in the Declaration only provides guidance for cell growth after 5 days. Therefore, this experiment does not provide guidance commensurate in scope with the claimed invention.

Example 2 of the Shinohara Declaration teaches that spermatogonial stem cells were dispersed by trypsin treatment, transferred onto 6 well plates and culture in F/SP medium supplemented with LIF and GDNF and that the number of spermatogonial stem cells were monitored sequentially for 30 days and the Declaration concludes that spermatogonial stem cells can grow in a medium containing GDNF and LIF without any other growth factors, for 30 days. This example is not fully persuasive because Example 1 of the Declaration discusses using “F/S medium” whereas Example 2 in the Declaration teaches using “F/SP medium”. It is unclear what the differences between F/S and F/SP medium are, with regard to specific components in the media. Therefore, Example 2 does not provide a clear nexus with regard to a media that only contains GDNF and LIF to

culture spermatogonial stem cells. Additionally, the Declaration does not provide any guidance with regard to utilizing neurturin or artemin under the same conditions that are described in the Declaration.

Accordingly, in view of the unpredictable state of the art of culturing spermatogonial stem cells, with regard to the viability of *in vitro* cultured SSCs, the lack of guidance or teachings provided by the specification for culture conditions of SSCs for 3-4 weeks, other than the exemplified conditions which require GDNF, LIF, bFGF, EGF and serum, the state of the art of SSCs, it would have required undue experimentation for the skilled artisan to make and use the full breadth of the claimed methods.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632